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ORIGINAL RESEARCH

Elevated Blood Alcohol Concentration at Stroke Onset Predicts Poor Clinical Outcomes and Mortality After Intracerebral Hemorrhage: A Retrospective Cohort Study

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ABSTRACT

***Introduction*:** The impact of acute alcohol consumption at the onset of spontaneous non-traumatic intracerebral hemorrhage (ICH) remains unclear. We evaluated the association between elevated blood alcohol concentration (BAC) at admission and clinical outcomes in patients with ICH.

***Methods*:** This retrospective single-center cohort study analyzed 1081 patients admitted with ICH between 2000 and 2023. BAC was measured at admission when alcohol use was suspected. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and the Glasgow Coma Scale (GCS). Outcomes—7-day neurological deterioration (ND), mortality, 90-day modified Rankin Scale (mRS) scores—were analyzed using logistic and Cox regression models to assess associations with acute alcohol consumption.

Zsuzsa Bagoly and László Oláh contributed equally to this work.

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***Results*:** Patients that were BAC positive (alcohol group; $n=31$, 2.9%) were younger, predominantly male, had larger hematoma volumes, showed significantly higher rates of 7-day ND (58.1% vs. 27.6%, $p<0.001$) and mortality at 7, 30, and 90 days (51.6% vs. 23.7%, 71% vs. 37.6%, 71% vs. 43.3%, all $p<0.001$) than patients with no clinical suspicion of alcohol consumption (control group; $n=1050$, 97.1%). Multivariable Cox regression identified elevated BAC as an independent predictor of mortality at all time points (HR 2.089, 95% CI 1.091–3.997, $p=0.026$ at 7 days; HR 2.133, 95% CI 1.220–3.728, $p=0.008$ at 30 days; HR 2.096, 95% CI 1.214–3.622, $p=0.008$ at 90 days). Multivariate logistic regression identified elevated BAC as an independent predictor of 7-day ND (OR 4.188, 95% CI 1.163–15.078, $p=0.028$) and large ICH volume (≥ 30 cm^3) (OR 3.67, 95% CI 1.388–9.704, $p=0.009$). In a subgroup analysis of heavy-drinking patients, elevated BAC was associated with early ND, increased mortality, and large ICH volume.
***Conclusion*:** Elevated BAC at ICH onset independently predicts early ND and increased mortality, indicating a potentially modifiable prognostic factor in acute ICH. These results underscore the importance of BAC measurement in patients with suspected alcohol consumption and warrant further research aimed at understanding and mitigating its potential detrimental effects.

Keywords: Blood alcohol concentration; Ethanol; Intracerebral hemorrhage; Mortality; Prognosis; Risk factors; Survival analysis

Key Summary Points

Why carry out this study?

While chronic alcohol intake is an established risk factor for spontaneous non-traumatic intracerebral hemorrhage (ICH), the short-term impact of elevated blood alcohol concentration (BAC) at the time of ICH onset has not been systematically evaluated.

This study aimed to clarify whether elevated BAC at admission is associated with clinical outcomes in patients with spontaneous non-traumatic ICH.

What was learned from the study?

Acute alcohol consumption, even at relatively low BAC levels (below 0.1%), was identified as an independent predictor of early neurological deterioration, increased mortality at 7, 30, and 90 days and increased hematoma volume (≥ 30 cm^3) on admission as estimated by non-contrast computed tomography.

These findings were further supported by a subgroup analysis limited to heavy drinkers with ICH, confirming that acute alcohol consumption exerts additional adverse effects even among chronically exposed patients.

These results highlight the need for routine BAC assessment in patients with suspected alcohol intake and support further studies exploring targeted interventions to mitigate alcohol-related harm in ICH.

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) accounts for approximately 20% of all stroke cases [1]. Previous studies have reported that mortality among patients with ICH is significantly higher than that among patients with acute ischemic stroke, with 30–40% of patients dying within the first month after ICH [2, 3]. Not only is mortality higher but functional outcomes are also unfavorable, as only 10–20% of

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patients with ICH live independently at 30 days after the event [4]. Although the treatment of acute ischemic stroke has dramatically improved over the last decades, only modest progress has been achieved in improving the treatment of hemorrhagic stroke [5, 6]. Therefore, given the limited effectiveness of current treatments for ICH, identifying reliable prognostic markers for early risk stratification remains a critical clinical priority.

Numerous studies have examined the effects of chronic alcohol consumption on cerebrovascular diseases. Regular heavy drinking has been identified as a risk factor for all stroke subtypes, including parenchymal hemorrhage [7]. In contrast, substantial and consistent evidence supports a protective association between low to moderate alcohol intake and ischemic stroke, while any level of alcohol consumption appears to increase the risk of hemorrhagic stroke, without evidence of a protective effect [7, 8]. In contrast to chronic exposure, limited data are available on the effects of acute alcohol intake during the early phase of cerebrovascular events. In animal models of transient focal cerebral ischemia, acute ethanol administration demonstrated neuroprotective effects without increasing the risk of ICH, even when combined with thrombolytic therapy [9, 10]. Furthermore, two pilot clinical trials showed that intravenous administration of caffeinol (a combination of ethanol and caffeine), either alone or alongside intravenous thrombolysis (IVT), was safe and feasible in patients with acute ischemic stroke. However, these studies included very few patients (≤ 25), and no control group was used; therefore the effect of caffeinol on IVT outcome could not be evaluated [11, 12]. The promising results of these studies prompted us to investigate IVT outcomes in patients with acute ischemic stroke under the acute influence of ethanol, using data from two large Hungarian stroke registries. In that study, we reported an association between elevated blood alcohol concentration (BAC) at arrival and improved short- and long-term outcomes following IVT in patients with acute ischemic stroke [13]. Moreover, elevated BAC at admission has been shown to exert neuroprotective effects not only in patients with acute ischemic stroke but also in those with traumatic brain injury (TBI) [14, 15]. In a retrospective cohort study, patients with severe TBI with low to moderate BAC on admission had lower mortality rates compared to patients with no or high BAC [14]. Another retrospective study demonstrated that mortality rate was significantly higher in BAC-negative patients with severe TBI as compared to patients that were BAC positive [15]. Although the underlying mechanisms remain incompletely understood, potential protective effects of alcohol may involve favorable hemodynamic alterations, modulation of hemostasis, and anti-apoptotic signaling pathways [16–20]. Nevertheless, such favorable effects of acute alcohol consumption may not apply to all stroke types. A preclinical study in a rat model of ICH demonstrated that excessive ethanol pretreatment exacerbated poor clinical outcomes, including increased mortality and neurological deficits, by promoting hematoma expansion [21].

Taken together, these data highlight a critical knowledge gap regarding the short-term impact of acute alcohol intake in spontaneous non-traumatic ICH. To our knowledge, no previous study has systematically investigated the impact of acute alcohol consumption on clinical outcomes in patients with ICH. To address this, we conducted a retrospective cohort study testing the hypothesis that elevated BAC at ICH onset is associated with larger hematoma volume, early neurological deterioration, and increased short-term mortality.

METHODS

Study Design

This single-center, retrospective cohort study analyzed consecutively admitted patients with spontaneous non-traumatic ICH. The study was based on a large, prospectively collected ICH registry and electronic medical records from a major Hungarian stroke center (Department of Neurology, University of Debrecen, Debrecen). The study protocol was approved by the Regional and Institutional Ethics Committee of the Clinical Centre of University of Debrecen (protocol number 6529-2023) and conducted in

accordance with the principles of the Declaration of Helsinki. Given the retrospective nature of the study, the need for informed consent was waived. All patients were evaluated by a neurologist, and the diagnosis of ICH was established by non-contrast cranial CT (NCCT). The inclusion criteria were as follows: a diagnosis of spontaneous non-traumatic ICH detected by NCCT, age ≥ 18 years, and hospital admission within 24 h of symptom onset. Exclusion criteria included a history of severe renal or liver dysfunction, hematological malignancy, secondary hemorrhage due to trauma, malignancy, aneurysm rupture, other vascular abnormalities, venous sinus thrombosis, or vasculitis, incomplete medical records and cases with suspected alcohol consumption (e.g., arriving from a pub or with documented acute alcohol consumption in their medical history) but no available BAC measurement at admission. Electronic medical records of patients with ICH admitted between January 2000 and May 2023 were reviewed to identify cases meeting the inclusion and exclusion criteria. Patients were categorized into two groups based on BAC measurement at admission. The alcohol group consisted of patients with confirmed acute alcohol consumption prior to stroke onset, defined by a detectable BAC upon admission. In most cases, BAC was measured when alcohol consumption was suspected or evident. The control group included patients who met the same eligibility criteria but had no clinical suspicion of alcohol consumption. This final study cohort was used to assess the association between elevated BAC and clinical outcomes in patients with spontaneous non-traumatic ICH.

Database

The following variables were recorded for all participants: demographics (age and sex); history of cerebrovascular and cardiovascular diseases (hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, ischemic heart disease, prior ischemic and hemorrhagic stroke); vascular risk factors (body mass index (BMI), smoking, chronic ethanol consumption); systolic and diastolic blood pressure at admission; medications at admission; onset-to-door time; detailed laboratory parameters (including electrolytes, glucose, liver- and renal function tests, C-reactive protein, complete blood count, hemostasis panel, BAC in the alcohol group) from admission blood samples; and admission imaging results. Stroke severity on admission was routinely assessed by National Institutes of Health Stroke Scale (NIHSS), while hypnoid disturbance of consciousness was evaluated by Glasgow Coma Scale (GCS). To predict the prognosis of the ICH, we calculated the ICH score for every participant on admission. ICH score was calculated on the basis of clinical data and CT findings, including age, GCS score, presence of intraventricular hemorrhage (IVH), ICH volume, and infratentorial location. As part of the prospective registry, a questionnaire was used to assess the cerebrovascular risk factors of patients, including alcohol consumption habits. In this questionnaire, patients (or their relatives if assistance was needed) were asked about the frequency, type, and amount of their weekly alcohol consumption. Alcohol intake was calculated and expressed in grams of ethanol per week. On the basis of the amount of alcohol consumed, patients were classified as non-drinkers (0 g/week), mild (less than 105 g/week), moderate (at least 105 but less than 210 g/week), and heavy drinkers (at least 210 g/week) [22]. Patients who had smoked at least one cigarette/day within the past 3 months of admission were classified as current smokers [23]. The autopsy rate at our clinical center was approximately 80% during the study period [24]. Autopsies were omitted only if the cause of death was deemed clinically evident. All patients were anonymized; authors had no access to personally identifiable information during or after data collection.

Neuroimaging

All participants underwent NCCT at admission. In cases where venous sinus thrombosis, arteriovenous shunts, or aneurysms were suspected as the underlying cause of an atypical intraparenchymal hemorrhage, additional imaging was performed, including arterial and venous computed tomographic angiography (CTA),

venography, or digital subtraction angiography (DSA). When the possibility of brain malignancies or cavernous malformations arose as the underlying cause of hemorrhage, brain magnetic resonance imaging (MRI) was performed. Hematoma volume at admission was calculated using the ellipsoid formula ($ABC/2$), where A is the largest hemorrhage diameter, B is the diameter perpendicular to A, and C equals the number of CT slices affected multiplied by slice thickness. The volume extended to the ventricles was not included in the hematoma volume calculation [25]. Hematoma location was also evaluated and divided into lobe, deep in brain (basal ganglia and thalamus), cerebellar and brainstem hemorrhage. Hydrocephalus was defined as increased radius or decreased ventricular angle in frontal horns, rounding and enlargement of atrium with sulcal effacement, increased width of third ventricle, or ballooning of fourth ventricle [26]. The degree of midline shift (MLS) was determined by measuring the maximal displacement of the septum pellucidum across the midline, using a perpendicular line connecting the anterior and posterior insertions of the falx cerebri at the level of the foramen of Monro as a reference [27]. Subjects were dichotomized according to whether the MLS was ≥ 5 mm. The presence of subarachnoid hemorrhage and intraventricular extension was also recorded. Three experienced radiologists who were blinded to clinical and laboratory data independently analyzed the images. In case of discrepancies a second consensus analysis was performed.

Outcome Measures

The primary short-term outcome was assessed by the neurological deterioration (ND) within the first 7 days following the onset of ICH. According to previous literature, ND was defined as an increase of at least 4 points in the NIHSS score or a decrease of at least 2 points in the GCS score within the first 7 days of the hospitalization [28]. If a patient died during this period, they were automatically classified as having ND. The primary long-term outcome was evaluated using the modified Rankin Scale (mRS) score at 90 days post ICH onset. A favorable outcome was defined as an mRS score of 0–2, whereas an unfavorable outcome was defined as an mRS score of 3–6. Mortality was assessed at 7, 30, and 90 days. To further investigate the potential mechanisms of alcohol-related outcome differences, predefined subgroup analysis was performed. In the first analysis, hematoma volume was dichotomized into two categories (< 30 cm^3 and ≥ 30 cm^3), based on prior studies identifying this threshold as a strong predictor of mortality [29–31]. The association between elevated BAC and hematoma size was analyzed using multivariate logistic regression models. Additionally, a separate subgroup analysis was conducted among heavy-drinking patients with spontaneous non-traumatic ICH to explore outcome associations within a more homogenous population in terms of alcohol use patterns.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Release 26.0, Chicago, IL), and GraphPad Prism 8.0 (GraphPad Prism Inc., La Jolla, CA). The Shapiro–Wilk test was used to assess the normality of continuous variables. Student's t test or Mann–Whitney U test was performed for independent two-group analyses. Differences between categorical variables were assessed by χ^2 test or Fisher's exact test, as appropriate. Kaplan–Meier survival analyses were performed to compare mortality rates between patients with elevated BAC and controls upon admission, including subgroup comparisons among heavy drinkers. Group differences were tested using the log-rank test. Multivariate logistic regression analyses were used to evaluate independent predictors of ND by day 7 and large hematoma volume (hematoma volume ≥ 30 cm^3). In the subgroup of heavy-drinking patients, additional multivariate logistic regression models were constructed to explore the association between elevated BAC and clinical outcomes (neurological deterioration by day 7, mortality, and larger hematoma volume ≥ 30 cm^3) within a subgroup characterized by homogeneous patterns of habitual alcohol consumption. Results of the logistic regression analysis were expressed

as odds ratios (OR) and 95% confidence intervals (CI). To examine the association between elevated BAC and mortality at 7, 30, and 90 days in the full cohort, Cox proportional hazards regression models were constructed, reporting HRs and 95% CIs. Adjustments of the models were based on the results of preliminary statistical analyses of baseline characteristics between groups (Student's t test or Mann–Whitney U test, χ^2 test or Fisher's exact), literature data, and methodological principles. Statistical significance was assumed with a p value of <0.05 in all analyses.

RESULTS

Baseline Characteristics of the Participants

Data from 1572 patients were retrospectively collected. We excluded 321 patients with secondary ICH due to aneurysm, trauma, arteriovenous malformation, cavernous hemangioma, venous malformation, venous sinus thrombosis, or vasculitis as well as 14 patients with primary IVH. In addition, 65 patients with chronic renal failure, chronic liver disease, or hematological malignancies at admission were also excluded from the analysis. An additional 94 patients were excluded because of missing medical data, and 11 others were excluded because alcohol consumption was suspected prior to stroke onset, but BAC was not measured. Ultimately, 1081 patients with spontaneous ICH were included in the final analysis, of whom 31 had an elevated BAC at the time of hospital admission (Fig. 1). Of the 1081 patients, 615 (56.9%) were male and 466 (43.1%) were female.

Table 1 presents the baseline and clinical characteristics of the study population. The median age was significantly lower, and the proportion of men was significantly higher in the alcohol group compared to the control group. Patients in the alcohol group had significantly higher NIHSS scores and lower GCS scores on admission. The prevalence of major cerebrovascular risk factors did not differ significantly between the two groups, except for coronary heart disease, which was less common in the

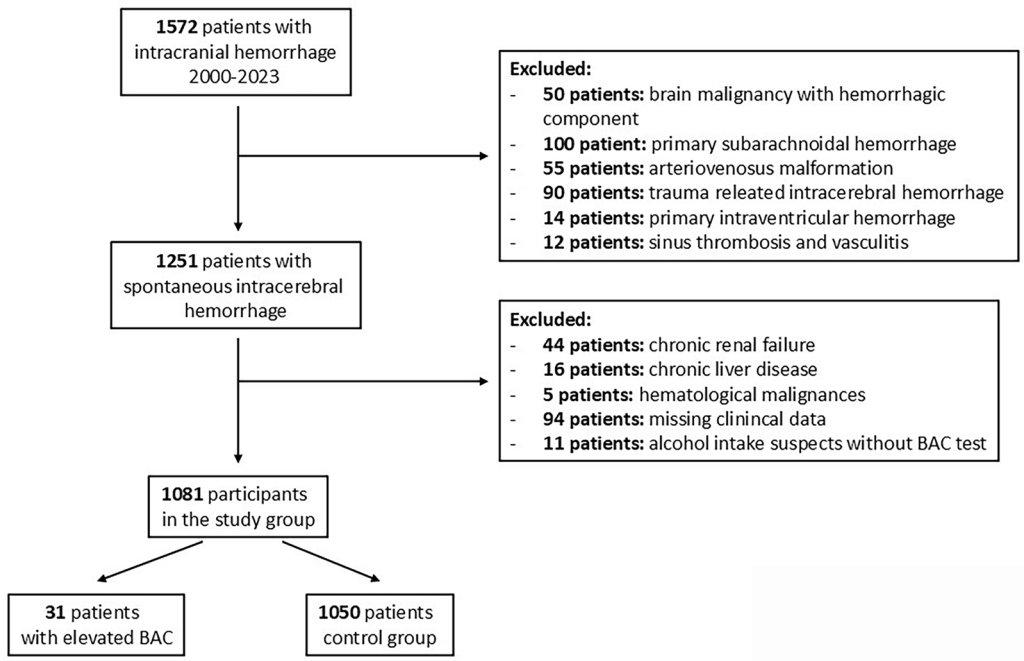

Fig. 1 Flowchart of cohort selection. A flow diagram presenting the number of patients included and excluded at each step of the study

Table 1 Baseline characteristics of cases (alcohol group) and controls

Variables	Total	Alcohol group	Control group	*p* value
Number of patients, *n* (%)	1081	31 (2.9%)	1050 (97.1%)	
Demographics				
Male, *n* (%)	615 (56.9%)	27 (87.1%)	588 (56.9%)	0.001*
Age (years), median (IQR)	69 (59–78)	57 (53–67)	69 (59–78)	< 0.001*
Clinical presentation on admission				
NIHSS on admission, median (IQR)	13 (7–21)	18 (14–24)	13 (7–21)	0.019*
GCS on admission, median (IQR)	12 (9–14)	9 (5–13)	12 (9–14)	0.012*
ICH score on admission, median (IQR)	2 (1–3)	3 (1–3)	2 (1–3)	0.121
ODT (h), median (IQR)	2.3 (1.5–4.6)	2.1 (1.5–3.0)	2.3 (1.5–4.7)	0.307
Admission systolic BP (mmHg), median (IQR)	182 (160–210)	199 (161–210)	182 (160–210)	0.439
Admission diastolic BP (mmHg), median (IQR)	100 (89–111)	107 (93–116)	100 (88.5–110)	0.037*
Cerebrovascular risk factors				
Hypertension, *n* (%)	1057 (97.8%)	30 (96.8%)	1027 (97.8%)	0.700
Diabetes mellitus, *n* (%)	289 (26.7%)	4 (12.9%)	285 (27.1%)	0.077
Hyperlipidemia, *n* (%)	302 (27.9%)	4 (12.9%)	298 (28.4%)	0.058
Atrial fibrillation, *n* (%)	149 (13.8%)	2 (6.5%)	147 (14%)	0.230
Coronary heart disease, *n* (%)	338 (31.3%)	3 (9.7%)	335 (31.9%)	0.009*
History of ischemic stroke, *n* (%)	191 (17.7%)	4 (12.9%)	187 (17.8%)	0.480
History of hemorrhagic stroke, *n* (%)	45 (4.2%)	1 (3.2%)	44 (4.2%)	0.791
BMI, median (IQR)	26.8 (23.2–31.1)	25.0 (22.5–29.7)	27.0 (23.2–31.2)	0.194
Current smoker, *n* (%)	230 (24.1%)	16 (55.2%)	214 (23.2%)	< 0.001*
Alcohol consumption habits, *n* (%)				
Non-drinker	523 (54.3%)	0 (0%)	523 (56.1%)	< 0.001*
Mild drinker	88 (9.1%)	6 (19.4%)	82 (8.8%)	
Moderate drinker	25 (2.6%)	1 (3.2%)	24 (2.6%)	
Heavy drinker	328 (34%)	24 (77.4%)	304 (32.6%)	
Medication at admission, *n* (%)				
Antihypertension therapy	541 (52.6%)	3 (9.7%)	538 (54%)	< 0.001*
Antidiabetic medications	152 (15%)	0 (0%)	152 (15.4%)	0.018*
Lipid-lowering therapy	167 (16.3%)	0 (0%)	167 (16.8%)	0.013*
Antiplatelet therapy	197 (19.3%)	3 (9.7%)	194 (19.6%)	0.168
Oral anticoagulants	93 (9.1%)	0 (0%)	93 (9.4%)	0.074

Table 1 continued

Variables	Total	Alcohol group	Control group	*p* value
Baseline NCCT findings				
Location, *n* (%)				
Deep	616 (57.1%)	13 (41.9%)	603 (57.5%)	0.074
Lobar	366 (33.9%)	17 (54.8%)	349 (33.3%)	
Brainstem	49 (4.55%)	1 (3.2%)	48 (4.6%)	
Cerebellum	48 (4.45%)	0 (0%)	48 (4.6%)	
Intraventricular extension, *n* (%)	472 (43.9%)	17 (54.8%)	455 (43.5%)	0.212
Presence of hydrocephalus, *n* (%)	143 (13.3%)	6 (19.4%)	137 (13.1%)	0.310
Presence of SAH, *n* (%)	102 (9.5%)	0 (0%)	102 (9.7%)	0.068
Midline shift ≥ 5 mm, *n* (%)	250 (23.1%)	16 (51.6%)	234 (22.3%)	< 0.001*
ICH volume (mL), median (IQR)	13.3 (4.3–40.5)	68.6 (9.1–100.6)	12.9 (4.2–37.8)	0.002*
Laboratory parameters at admission, median (IQR)				
Serum ethanol (%) level		0.07 (0.02–0.12)		
Serum sodium (mmol/L)	140 (138–142)	140 (137–141)	140 (138–142)	0.129
Serum glucose (mmol/L)	7.5 (6.1–9.7)	6.8 (5.9–7.8)	7.5 (6.1–9.8)	0.068
Creatinine (μmol/L)	70 (58–85)	64 (48–81)	70 (58–85)	0.091
hsCRP (mg/L)	3.0 (1.3–6.7)	2.7 (0.7–7.7)	3 (1.3–6.7)	0.432
AST (U/L)	24 (19–33)	57 (33–101)	23 (18–32)	< 0.001*
ALT (U/L)	19 (14–29)	41.5 (23–82)	19 (14–27)	< 0.001*
GGT (U/L)	32 (19–76)	155.5 (76.5–374.5)	31 (19–69)	< 0.001*
WBC (G/L)	9.1 (6.9–11.9)	8.3 (6.5–10.2)	9.1 (6.9–12.1)	0.128
Hemoglobin (g/L)	141 (130–150)	145 (134–154)	141 (130–150)	0.179
Platelet count (G/L)	208 (170–255)	179 (132–247)	209 (170–256)	0.026*
INR	0.99 (0.94–1.07)	0.98 (0.93–1.05)	0.99 (0.94–1.07)	0.679
APTI (s)	29 (26–33)	30 (27–32)	29 (26–33)	0.617

Unless otherwise indicated, data are medians (interquartile rangers) or numbers (percentage)

IQR interquartile range, *NIHSS* National Institute of Health Stroke Scale, *GCS* Glasgow Coma Scale, *ICH score* intracerebral hemorrhage score, *ODT* onset to door time, *BP* blood pressure, *BMI* body mass index, *NCCT* non-contrast computer tomography, *SAH* subarachnoid hemorrhage, *hsCRP* high-sensitivity C-reactive protein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyl transferase, *WBC* white blood cell, *APTT* activated partial thromboplastin time, *INR* international normalized ratio

*Statistically significant difference ($p < 0.05$)

alcohol group in comparison with controls. As expected, smoking and moderate-to-heavy alcohol use were significantly more prevalent among patients in the alcohol group. Although the rates of hypertension, diabetes mellitus, and hyperlipidemia were similar in both groups, the use of antihypertensive, antidiabetic, and lipid-lowering medications was significantly lower in the alcohol group, indicating a higher rate of untreated conditions. As anticipated, patients in the alcohol group exhibited significantly higher serum levels of alanine transaminase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT), and significantly lower platelet counts compared to controls. While the prevalence of hydrocephalus, subarachnoid hemorrhage, and IVH on admission NCCT scans did not differ significantly between the two groups, the median hematoma volume was larger, and the presence of midline shift ≥ 5 mm was more common, in the alcohol group.

Influence of Acute Alcohol Consumption on Clinical Outcomes

ND by day 7 occurred significantly more often in the alcohol group compared to the control group (58.1% vs. 27.6%, $p < 0.001$). Mortality rates at days 7, 30, and 90 were significantly higher in the alcohol group relative to the control group (51.6% vs. 23.7%, $p < 0.001$; 71% vs. 37.6%, $p < 0.001$; and 71% vs. 43.3%, $p = 0.002$, respectively). Thus, the elevated BAC in the patients with ICH more than doubled the risk of early death compared to controls. Favorable long-term outcome, defined as 90-day mRS score of 0–2, did not differ in patients with elevated BAC vs. controls (12.9% vs. 22.6%, $p = 0.202$) (Table 2).

To assess the time-dependent impact of acute alcohol consumption on mortality following ICH, Kaplan–Meier survival curves were generated for 90-day follow-up periods (Fig. 2). Participants with detectable BAC showed significantly lower survival at all time points as compared to controls (log-rank $p < 0.001$ by day 7, 30, 90). A marked early divergence of the survival curves was observed within the first few days post admission, indicating that the detrimental effect of alcohol consumption becomes apparent very early. The distribution of causes of death was also compared between the two groups (Table 2) and a significant difference was observed ($p = 0.014$). Cerebellar tonsillar herniation and brainstem hemorrhage were more frequent in the alcohol group as compared to the controls (68.2% vs. 53.3% and 13.6% vs. 5.3%, respectively), whereas non-cerebral complication-related deaths (pneumonia, sepsis, pulmonary embolism, myocardial infarction, cardiorespiratory insufficiency) were more common in controls (Table 2). Gastrointestinal hemorrhage as cause of death was more common in the alcohol group in comparison to the control group (4.6% vs. 0.2%). To further examine the potential effect of acute alcohol consumption on the fatal outcomes, causes of death were dichotomized into brain damage and non-cerebral complication-related death categories. Deaths caused by brain damage were defined as those resulting from cerebellar tonsillar herniation and brainstem damage, while non-cerebral complication-related deaths included all other causes listed in Table 2. The dichotomized categorization demonstrated that the rate of death caused by brain damage is significantly higher in the alcohol group than the control group (81.8% vs. 58.6%, $p = 0.043$).

To identify parameters associated with mortality at 7, 30, and 90 days in the investigated cohort, multivariable Cox proportional hazard regression analyses was used (Table 3). Results of univariate analysis revealing parameters that significantly influence mortality at 7, 30, and 90 days are shown in Supplementary Tables 1–3. According to multivariate Cox proportional hazard regression models including all relevant parameters (based on the results of univariate analysis, adjusting for history of chronic alcohol consumption), acute alcohol consumption was identified as a significant predictor of mortality at 7, 30, and 90 days (7-day mortality HR 2.089, 95% CI 1.091–3.997, $p = 0.026$; 30-day mortality HR 2.133, 95% CI 1.220–3.728, $p = 0.008$; and 90-day mortality HR 2.096, 95% CI 1.214–3.622, $p = 0.008$) (Table 3). To check the influence of elevated BAC on ND at 7 days, a multivariate logistic

Table 2 Outcome of cases (alcohol group) and controls

	Total	Alcohol group	Control group	*p* value
Neurological deterioration by day 7, *n* (%)	308 (28.5%)	18 (58.1%)	290 (27.6%)	< 0.001*
Mortality by day 7, *n* (%)	265 (24.5%)	16 (51.6%)	249 (23.7%)	< 0.001*
Mortality by day 30, *n* (%)	417 (38.6%)	22 (71%)	395 (37.6%)	< 0.001*
Mortality by day 90, *n* (%)	477 (44.1%)	22 (71%)	455 (43.3%)	0.002*
Long-term outcome, mRS, day 90, *n* (%)				
mRS 0–2	241 (22.3%)	4 (12.9%)	237 (22.6%)	0.202
mRS 3–6	840 (77.7%)	27 (87.1%)	813 (77.4%)	
Cause of death by day 90, *n* (%)				
Cerebellar tonsillar herniation	257 (54%)	15 (68.2%)	242 (53.3%)	0.014*
Brainstem hemorrhage	27 (5.7%)	3 (13.6%)	24 (5.3%)	
Pneumonia	104 (21.8%)	3 (13.6%)	101 (22.3%)	
Pulmonary embolism	25 (5.3%)	0 (0%)	25 (5.5%)	
Sepsis	22 (4.6%)	0 (0%)	22 (4.8%)	
Myocardial infarction	6 (1.3%)	0 (0%)	6 (1.3%)	
Cardiorespiratory insufficiency	33 (6.9%)	0 (0%)	33 (7.3%)	
Gastrointestinal hemorrhage	2 (0.4%)	1 (4.6%)	1 (0.2%)	
Cause of death by day 90, *n* (%)				
Brain damage	284 (59.7%)	18 (81.8%)	266 (58.6%)	0.043*
Non-cerebral complication-related death	192 (40.3%)	4 (18.2%)	188 (41.4%)	

Data are numbers (percentage)

mRS modified Rankin Scale

*Statistically significant difference ($p < 0.05$)

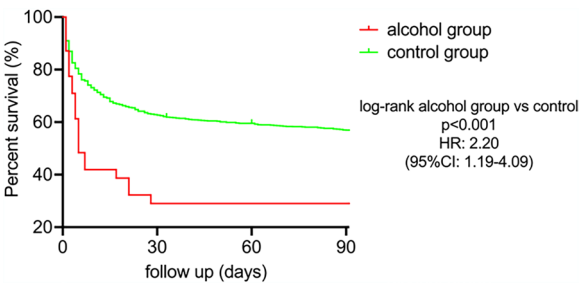

Fig. 2 Kaplan–Meier survival curves of patients with spontaneous intracerebral hemorrhage in the alcohol group and control group. Patients with elevated BAC showed significantly lower survival rates (log-rank test, $p < 0.001$)

regression analysis (including age, sex, BMI, atrial fibrillation, coronary heart diseases, antihypertension, lipid-lowering, antiplatelet therapy at admission, ICH volume, ICH location, presence of hydrocephalus and subarachnoid hemorrhage, GCS and NIHSS score at admission, serum glucose, creatinine and alanine transaminase, APTT, INR, hemoglobin at admission) was used (Table 4). Acute alcohol consumption remained a significant independent predictor of ND within 7 days in the multivariate model (OR 4.188, CI 1.163–15.078, $p = 0.028$).

Table 3 Cox proportional hazard regression to identify predictors of mortality by day 7, 30, and 90

	Mortality by day 7		Mortality by day 30		Mortality by day 90	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p* value
Age (per 1 year increase)	0.990 (0.974–1.006)	0.233	1.008 (0.996–1.021)	0.205	1.016 (1.004–1.028)	0.01*
Sex (male)	0.704 (0.480–1.033)	0.073	0.687 (0.503–0.938)	0.018*	0.649 (0.493–0.854)	0.002*
BMI (per 1 kg/m^2 increase)	0.972 (0.944–1.000)	0.052	0.980 (0.959–1.002)	0.077	0.978 (0.958–0.998)	0.034*
GCS on admission (per 1 point decrease)	0.867 (0.818–0.920)	< 0.001*	0.835 (0.800–0.872)	< 0.001*	0.834 (0.801–0.867)	< 0.001*
Acute alcohol consumption	2.089 (1.091–3.997)	0.026*	2.133 (1.220–3.728)	0.008*	2.096 (1.214–3.6220)	0.008*
Alcohol consumption habits (heavy drinkers vs. non, mild, moderate drinkers)	0.890 (0.769–1.029)	0.116	0.968 (0.865–1.084)	0.576	0.978 (0.881–1.085)	0.669
Prior diabetes mellitus	–	–	–	–	0.922 (0.651–1.305)	0.646
Prior atrial fibrillation	0.739 (0.425–1.285)	0.284	0.697 (0.449–1.081)	0.107	0.726 (0.489–1.077)	0.112
Prior coronary heart disease	1.397 (0.943–2.069)	0.095	1.123 (0.833–1.514)	0.445	1.071 (0.813–1.409)	0.627
Prior antihypertension therapy	–	–	1.319 (0.984–1.769)	0.064	1.437 (1.097–1.883)	0.009*
Prior lipid-lowering therapy	1.034 (0.649–1.647)	0.888	1.047 (0.734–1.492)	0.801	0.959 (0.689–1.333)	0.802
Prior antiplatelet treatment	–	–	0.997 (0.713–1.394)	0.987	1.073 (0.791–1.455)	0.652
Prior oral anticoagulants	1.192 (0.639–2.222)	0.581	0.960 (0.576–1.600)	0.876	1.159 (0.733–1.833)	0.529
ICH location on baseline NCCT (deep ICH vs. lobar, cerebellar, brainstem ICH)	1.262 (1.004–1.586)	0.046*	1.167 (0.981–1.389)	0.080	1.126 (0.958–1.324)	0.150
ICH volume (per 1 cm^3 increase)	1.011 (1.008–1.015)	< 0.001*	1.011 (1.008–1.014)	< 0.001*	1.011 (1.008–1.013)	< 0.001*

Table 3 continued

	Mortality by day 7		Mortality by day 30		Mortality by day 90	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p* value
Intraventricular extension	1.491 (0.960–2.318)	0.076	1.317 (0.957–1.811)	0.091	1.348 (1.008–1.802)	0.044*
Presence of hydrocephalus	1.601(1.050–2.442)	0.029*	1.658 (1.173–2.341)	0.004*	1.659 (1.197–2.299)	0.002*
Presence of SAH	1.807 (1.153–2.832)	0.010*	1.823 (1.267–2.624)	0.001*	1.603 (1.130–2.274)	0.008*
Serum glucose (per 1 mmol/L increase)	1.044 (0.991–1.099)	0.106	1.016 (0.976–1.058)	0.437	1.043 (0.998–1.090)	0.059
Creatinine (per 1 μmol/L increase)	–	–	1.002 (0.997–1.008)	0.381	–	–
AST (per 1 U/L increase)	1.002 (0.998–1.007)	0.319	1.002 (0.998–1.005)	0.294	1.002 (0.998–1.005)	0.324
ALT (per 1 U/L increase)	1.001 (0.998–1.003)	0.481	–	–	–	–
WBC (per 1 G/L increase)	1.010 (0.964–1.058)	0.675	0.987 (0.951–1.024)	0.478	0.991 (0.958–1.024)	0.581
Hemoglobin (per 1 g/L decrease)	–	–	1.003 (0.994–1.012)	0.510	1.003 (0.995–1.011)	0.458
APTT (per 1 s prolongation)	1.018 (0.999–1.038)	0.063	1.023 (1.007–1.040)	0.005*	1.024 (1.007–1.040)	0.004*
INR (per 0.1 increase)	1.027 (0.823–1.281)	0.816	0.934 (0.775–1.127)	0.477	0.903 (0.756–1.079)	0.263

CI confidence interval, *HR* hazard ratio, *BMI* body mass index, *GCS* Glasgow Coma Scale, *ICH* intracerebral hemorrhage, *NCCT* non-contrast computer tomography, *SAH* subarachnoid hemorrhage, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *WBC* white blood cell, *APTT* activated partial thromboplastin time, *INR* international normalized ratio

*Statistically significant difference ($p < 0.05$)

Subgroup Analysis: Association Between Acute Alcohol Consumption and Hematoma Volume

On the basis of predefined subgrouping criteria described in the "Methods" section under outcome measures, we examined whether elevated BAC was associated with increased hematoma volume in patients with ICH. Results of univariate analysis revealing significant differences between patients with ICH volume < 30 and ≥ 30 cm^3 are shown in Table 5. According to multivariate logistic regression models including all relevant parameters (sex, age, BMI, prior anticoagulants treatment, white blood cell, glucose, AST, INR, adjusting for history of chronic alcohol consumption), acute alcohol consumption was identified as a significant predictor of increased hematoma volume (hematoma volume ≥ 30 cm^3), (OR 3.670, 95% CI 1.388–9.704, $p = 0.009$) (Table 6). In addition to acute alcohol consumption, older age (OR 1.017, 95% CI 1.001–1.033, $p = 0.036$), higher white blood cell count at admission

Table 4 Factors associated with 7-day neurological deterioration (ND) following ICH

ND by 7 days	OR	95% CI	*p* value
Acute alcohol consumption	4.188	1.163–15.078	0.028*
Alcohol consumption habits (heavy drinker vs. non, mild, moderate drinker)	0.828	0.671–1.021	0.078
GCS on admission (per 1 point decrease)	0.851	0.792–0.915	< 0.001*
Presence of hydrocephalus	2.680	1.353–5.310	0.0058
ICH volume (per 1 cm^3 increase)	1.022	1.015–1.029	< 0.001*
Sex (male)	0.520	0.288–0.939	0.030*
Age (per 1 year increase)	1.004	0.983–1.026	0.703
BMI (per 1 kg/m^2 increase)	0.991	0.954–1.030	0.660
Prior atrial fibrillation	0.688	0.310–1.529	0.359
Prior chronic heart diseases	1.080	0.625–1.866	0.782
Antihypertension therapy on admission	1.517	0.871–2.641	0.141
Lipid-lowering therapy on admission	0.825	0.419–1.626	0.578
Antiplatelet therapy on admission	1.803	0.960–3.385	0.067
Oral anticoagulants on admission	0.708	0.246–2.038	0.522
ICH location on baseline NCCT (deep ICH vs. lobar, cerebellar, brainstem ICH)	1.329	0.98–1.804	0.068
Presence of intraventricular extension	1.738	1.24–2.950	0.041*
Presence of SAH	1.970	0.986–3.934	0.055
Serum glucose on admission (per 1 mmol/L increase)	1.045	0.975–1.120	0.210
Serum creatinine on admission (per 1 μmol/L increase)	0.998	0.988–1.008	0.713
AST (per 1 U/L increase)	1.004	0.997–1.011	0.279
WBC count on admission (per 1 G/L increase)	0.996	0.933–1.063	0.909
Hemoglobin level on admission (per 1 g/L decrease)	1.002	0.986–1.018	0.813
APTT (per 1 s prolongation)	1.043	0.996–1.018	0.074
INR (per 0.1 increase)	1.058	0.663–1.686	0.814

Neurological deterioration was defined as at least 4 points increase of NIHSS or mortality in the first 7 days of hospital care. Multiple regression analyses included age, sex, acute alcohol consumption, GCS score on admission, alcohol consumption habits (heavy drinkers vs. non, mild, moderate drinkers), BMI, prior atrial fibrillation and chronic heart disease, prior antihypertension, lipid-lowering, antiplatelet therapy, oral anticoagulants, presence of hydrocephalus, presence of intraventricular extension, presence of SAH, ICH location on baseline NCCT, ICH volume, chronic ethanol consumption, serum glucose and creatinine on admission, AST, WBC, hemoglobin, APTT, INR level

OR odds ratio, *GCS* Glasgow Coma Scale, *ICH* intracerebral hemorrhage, *ICH score* intracerebral hemorrhage score, *BMI* body mass index, *NCCT* non-contrast computer tomography, *SAH* subarachnoid hemorrhage, *AST* aspartate aminotransferase, *WBC* white blood cell, *APTT* activated partial thromboplastin time, *INR* international normalized ratio

*Statistically significant difference ($p < 0.05$)

Table 5 Comparison of baseline demographic, clinical, and laboratory characteristics between patients with hematoma volume < 30 and ≥ 30 cm^3

Variables	Hematoma volume < 30 cm^3	Hematoma volume ≥ 30 cm^3	*p* value
Number of patients, *n* (%)	665	308	
Male, *n* (%)	369 (55.5%)	183 (59.4%)	0.250
Age (years), median (IQR)	68 (59–78)	71 (59–79)	0.101
onset to door time (h), median (IQR)	2.2 (1.5–4.6)	2.3 (1.5–4.3)	0.931
BMI, median (IQR)	27.3 (23.3–31.3)	26.2 (22.8–29.7)	0.018*
Systolic BP (mmHg), median (IQR)	180 (160–207)	185 (163.5–216)	0.086
Diastolic BP (mmHg), median (IQR)	100 (89–110)	100 (87–114)	0.301
NIHSS on admission, median (IQR)	10 (5–16)	21 (15–31)	< 0.001*
GCS on admission, median (IQR)	13 (11–15)	9 (4–12)	< 0.001*
Acute alcohol consumption, *n* (%)	10 (1.5%)	17 (5.5%)	< 0.001*
Current smoker, *n* (%)	140 (23.4%)	65 (24.6%)	0.691
Alcohol consumption habits, *n* (%)			
Non-drinker	346 (57.8%)	143 (52.6%)	
Mild drinker	56 (9.3%)	22 (8.1%)	0.135
Moderate drinker	18 (3%)	5 (1.8%)	
Heavy drinker	179 (29.9%)	102 (37.5%)	
Prior hypertension, *n* (%)	646 (97.1%)	303 (98.4%)	0.248
Prior diabetes mellitus, *n* (%)	174 (26.2%)	79 (25.7%)	0.864
Prior hyperlipidemia, *n* (%)	193 (29%)	80 (26%)	0.325
Prior atrial fibrillation, *n* (%)	89 (13.4%)	47 (15.3%)	0.432
Prior coronary heart disease, *n* (%)	197 (29.6%)	109 (35.4%)	0.072
History of ischemic stroke, *n* (%)	128 (19.3%)	54 (17.5%)	0.523
History of hemorrhagic stroke, *n* (%)	32 (4.8%)	10 (3.3%)	0.264
Prior antihypertension therapy, *n* (%)	339 (52.8%)	153 (53.5%)	0.845
Prior antidiabetic medications, *n* (%)	100 (15.8%)	41 (14.5%)	0.625
Prior lipid-lowering therapy, *n* (%)	102 (15.9%)	48 (16.9%)	0.707
Prior antiplatelet treatment, *n* (%)	126 (19.8%)	62 (21.8%)	0.469
Prior oral anticoagulants, *n* (%)	52 (8.1%)	36 (12.6%)	0.003*
Admission laboratory values, median (IQR)			
Serum sodium (mmol/L)	140 (139–142)	140 (138–142)	0.126
Serum glucose (mmol/L)	7 (5.8–9.3)	8.5 (6.9–10.5)	< 0.001*

Table 5 continued

Variables	Hematoma volume < 30 cm^3	Hematoma volume ≥ 30 cm^3	*p* value
Serum creatinine (μmol/L)	70 (58–84)	69 (58–87)	0.511
Serum hsCRP (mg/L)	3.0 (1.3–6.3)	3.0 (1.3–7.8)	0.709
Serum AST (U/L)	23 (17–31)	25 (20.5–36.5)	< 0.001*
Serum ALT (U/L)	18 (14–27)	18 (14–28)	0.970
Serum GGT (U/L)	30 (18–72.5)	32.5 (19–78)	0.351
WBC (G/L)	8.5 (6.7–11.0)	10.4 (7.9–13.4)	< 0.001*
Hemoglobin (g/L)	142 (131–151)	139 (126–149)	0.002*
Platelet count (G/L)	213 (173–260)	208 (162–250)	0.050
INR	0.98 (0.93–1.05)	1.00 (0.96–1.11)	< 0.001*
APTT (s)	28 (26–32)	29 (26–34)	0.084

IQR interquartile range, *NIHSS* National Institute of Health Stroke Scale, *GCS* Glasgow Coma Scale, *ICH score* intracerebral hemorrhage score, *ODT* onset to door time, *BP* blood pressure, *BMI* body mass index, *NCCT* non-contrast computer tomography, *SAH* subarachnoid hemorrhage, *hsCRP* high-sensitivity C-reactive protein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyl transferase, *WBC* white blood cell, *APTT* activated partial thromboplastin time, *INR* international normalized ratio

*Statistically significant difference ($p < 0.05$)

(OR 1.126, 95% CI 1.076–1.180, $p < 0.0001$), and elevated serum glucose level at admission (OR 1.059, 95% CI 1.010–1.111, $p = 0.018$) were also significantly associated with an increased risk of larger hematoma volume (Table 6). Conversely, higher hemoglobin level at admission (OR 0.977, 95% CI 0.966–0.989, $p < 0.001$) and male gender (OR 0.649, 95% CI 0.438–0.962, $p = 0.031$) were identified as significant protective factors against larger hematoma volume (Table 6).

Subgroup Analysis: Outcomes in Heavy-Drinking Patients with Intracerebral Hemorrhage

To better understand the etiological role of acute alcohol consumption in ICH outcomes, we conducted a subgroup analysis limited to heavy drinkers, representing a population homogeneous in habitual alcohol use. This approach allowed us to disentangle the acute effects of elevated BAC from the chronic impact of long-term heavy drinking. In this analysis, 24 heavy-drinking participants were classified as patients with elevated BAC while 304 heavy drinkers without evidence of acute alcohol influence served as controls. Supplementary Tables 4 and 5 show the baseline and clinical characteristics and clinical outcomes of this heavy-drinking cohort. Patients that were BAC positive present more severe baseline stroke severity and larger hematoma volume compared to control group (Table S4). ND at 7 days and mortality at all times were significantly higher among participants in the BAC positive group relative to controls (Table S5). Kaplan–Meier analysis confirmed markedly reduced cumulative survival among patients that were BAC positive (log-rank $p < 0.001$, Supplementary Fig. 1). In this subgroup analysis we also examined the distribution of cause of death and found that death caused by brain damage is significantly higher in the BAC positive group than in the control group (88.9% vs. 54.4%, $p = 0.005$; Table S5). In multivariate logistic regression models (Tables S6–S9) elevated BAC in the heavy drinking cohort independently predicts 7-day ND (OR 6.18,

Table 6 Independent factors for larger ICH hematoma (ICH volume ≥ 30 cm^3) in the investigated cohort

Hematoma volume ≥ 30 cm^3	OR	95% CI	*p* value
Sex (male)	0.649	0.438–0.962	0.031*
Age (per 1 year increase)	1.017	1.001–1.033	0.036*
Acute alcohol consumption	3.670	1.388–9.704	0.009*
Alcohol consumption habits (heavy drinker vs. non, mild, moderate drinker)	1.102	0.951–1.276	0.197
ODT (per 1 h increase)	0.985	0.947–1.025	0.462
Diastolic BP (mmHg) on admission (per 1 mmHg increase)	1.005	0.995–1.015	0.311
Prior oral anticoagulants	1.236	0.636–2.404	0.532
Serum glucose on admission (per 1 mmol/L increase)	1.059	1.010–1.111	0.018*
Serum AST (per 1 U/L increase)	1.006	1.000–1.013	0.057
Hemoglobin (per 1 g/L decrease)	0.977	0.966–0.989	< 0.001*
WBC (per 1 G/L increase)	1.126	1.076–1.180	< 0.001*
INR (per 0.1 unit increase)	1.211	0.991–1.479	0.062

Last step of multiple logistic regression analysis is provided. The definition of larger ICH hematoma was met when the ICH volume baseline NCCT was ≥ 30 cm^3. Backward multiple regression model included sex, age, acute alcohol consumption, alcohol consumption habits (heavy drinker vs. non, mild, moderate drinker), INR, WBC, hemoglobin, serum glucose on admission, serum AST, ODT, admission diastolic BP, prior oral anticoagulants

ICH intracerebral hemorrhage, *ODT* onset to door time, *BP* blood pressure, *AST* aspartate aminotransferase, *WBC* white blood cell, *INR* international normalized ratio

*Statistically significant difference ($p < 0.05$)

95% CI 2.38–16.07, $p < 0.001$), 7-day mortality (OR 5.16, 95% CI 2.07–12.85, $p < 0.001$), 30-day mortality (OR 10.11, 95% CI 3.42–29.91, $p < 0.001$), 90-day mortality (OR 9.51, 95% CI 3.16–28.57, $p < 0.001$), and larger hematoma volume (≥ 30 cm^3) (OR 3.39, 95% CI 1.24–9.23, $p = 0.017$).

DISCUSSION

This study is, to our knowledge, the first to demonstrate that acute alcohol consumption at the onset of ICH is independently associated with early neurological deterioration and increased mortality. Patients with elevated BAC in this cohort had larger hematoma volumes, more severe neurological status, and significantly higher rates of death compared to controls. Importantly, these associations remained significant after adjustment for chronic alcohol use, suggesting that acute alcohol exposure is an independent prognostic factor in spontaneous ICH. These findings are further supported by our subgroup analysis conducted among heavy drinkers, which confirmed the detrimental effect of acute alcohol consumption within a population homogeneous in habitual alcohol use. From a clinical perspective, BAC measurement at admission may therefore provide a simple and readily available tool for early risk stratification in patients with ICH.

A major strength of this work is the size and quality of the cohort. More than 1000 patients with ICH were analyzed from a single high-volume tertiary stroke center over a period of more than two decades. The availability of detailed

clinical, laboratory, and imaging data, combined with a high autopsy rate, provides a robust and reliable dataset highlighting the independent detrimental effects of alcohol consumption in patients with ICH. Importantly, the robustness of these findings was further supported by a dedicated subgroup analysis restricted to heavy-drinking patients with ICH, in whom the adverse impact of acute alcohol consumption persisted despite a shared background of chronic alcohol exposure. Within this well-characterized cohort, acute alcohol intake was linked to significantly larger hematoma volumes, higher rates of early neurological deterioration, and increased short-term mortality. These findings not only add new knowledge to the field but also emphasize the value of systematic BAC testing in the emergency evaluation of ICH, with potential to aid monitoring and management decisions.

In line with our findings, experimental animal studies have already suggested a dose-dependent effect of alcohol, with high-dose ethanol pretreatment worsening ICH outcomes, while some contradictory reports indicated that moderate preconditioning may attenuate oxidative stress and apoptosis [21, 22, 32]. In this study we clearly show that in patients with ICH even relatively low BAC values, such as the median of 0.07% observed here, are sufficient to worsen outcomes. Naturally, it cannot be ruled out that actual BAC levels at stroke onset were even higher and declined by the time patients reached the hospital. Despite this potential underestimation, even the measured BAC values at admission remained strongly associated with larger hematoma volumes, early neurological deterioration, and increased mortality, underscoring the clinical relevance of acute alcohol exposure in ICH. These results also point out the translational gap between standardized animal models and the complex reality of human ICH, where hematoma expansion is dynamic and influenced by multiple comorbidities.

Several pathophysiological mechanisms may explain the observed effects. Alcohol impairs platelet function and enhances fibrinolysis, which may facilitate hematoma growth [18, 33, 34]. In line with these findings, we have previously shown that in patients with acute ischemic stroke, acute alcohol intake improved the inefficacy rate of intravenous thrombolysis and was dose-dependently associated with better clinical outcomes [13]. On the other hand, the pathophysiological effects of ethanol and its metabolites may be detrimental in hemorrhagic stroke, promoting oxidative stress, red blood cell hemolysis, and amplifying secondary brain injury [35–42]. Hemodynamic factors may also play a role: while studies in animal models have reported ethanol-induced hypotension [42], patients in the current cohort with detectable BAC presented with higher diastolic blood pressure, which could accelerate hematoma expansion. These processes are consistent with our observation that alcohol-positive patients had a significantly higher proportion of deaths attributable to direct brain damage, and with the early divergence of survival curves between groups.

The clinical implications of our study are substantial. While outcomes in the overall cohort were comparable to those of major ICH registries [43, 44], patients with elevated BAC fared considerably worse. Acute alcohol intake was identified as a predictor of large hematoma volume, a key determinant of early death. Routine BAC assessment in suspected cases may therefore serve as an easily obtainable prognostic marker, helping to identify patients at high risk of rapid deterioration and poor outcome. Whether interventions that accelerate ethanol clearance or reduce its neurotoxic and hemostatic effects might mitigate poor outcomes is an important and intriguing question for future studies. While no targeted therapy currently exists to counteract the acute neurotoxic and coagulopathic effects of ethanol in ICH, potential strategies may include pharmacological enhancement of ethanol metabolism, antioxidant therapy to reduce oxidative injury, or modulation of fibrinolytic pathways. Experimental approaches aimed at limiting ethanol-induced oxidative stress and vascular permeability may also provide future therapeutic directions.

Limitations

As with all clinical studies, our findings should be interpreted in the context of both their strengths and limitations. Despite the strengths

of a large and well-documented cohort, several limitations must be acknowledged. The retrospective, single-center design carries a risk of selection bias. Although patients with suspected but unmeasured alcohol intake were excluded, undetected exposure cannot be fully ruled out. The alcohol group was relatively small compared to the control group, which limited subgroup analyses. Variability in the timing and quantity of alcohol consumed may have introduced heterogeneity, and hematoma volumes were estimated using the *ABC*/2 formula, which may overestimate size [45].

CONCLUSION

In a large, well-documented cohort of patients with ICH, acute alcohol consumption was independently associated with larger hematoma volumes, early neurological deterioration, and increased mortality. These findings suggest that BAC is a clinically relevant, readily available prognostic marker and underscore the need for prospective multicenter studies to validate these results and to explore strategies aimed at mitigating the harmful effects of acute alcohol exposure in patients with ICH.

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Author Contributions. Tamás Árokszállási, Zsuzsa Bagoly, László Oláh, László Csiba and Tünde Csépány contributed to the conception and design of the study. Tamás Árokszállási, Eszter Balogh, Péter Juhász, Lilla Rácz, Gábor Fekete contributed to the data curation and preparation. CT imaging analysis was performed by Edit Boglárka Nagy, Máté Sik and Zsófia Fülesdi. Attila Nagy, Tamás Árokszállási, Rita Orbán-Kálmándi and Zsuzsa Bagoly were responsible for statistical analysis. Tamás Árokszállási and Rita Orbán-Kálmándi prepared the figures. Tamás Árokszállási, Anita Árokszállási, Zsuzsa Bagoly, László Oláh and László Csiba drafted and revised the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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Data Availability. All data relevant to the study are included in the manuscript and supplementary materials. The data that support the findings of this study are available from the corresponding author, Tamás Árokszállási (University of Debrecen Faculty of Medicine Department of Neurology, arokszallasi.tamas@med.unideb.hu), upon reasonable request.

Declarations

Conflict of Interest. Tamás Árokszállási, Attila Nagy, Eszter Balogh, Edit Boglárka Nagy, Máté Sik, Zsófia Fülesdi, Rita Orbán-Kálmándi, Anita Árokszállási, Péter Juhász, Gábor Fekete, Lilla Rácz, Tünde Csépány, László Csiba, Zsuzsa Bagoly and László Oláh declare that there are no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical Approval. This retrospective study involving human participants was reviewed and

approved by the Regional and Institutional Ethics Committee of the Clinical Centre of University of Debrecen (protocol number 6529-2023). As the observational data we used came from the ongoing cohort, our study did not harm patients or expose personal data, and only analyzed baseline characteristics and clinical outcomes; therefore, informed consent was waived. This study was conducted in accordance with the Declaration of Helsinki.

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